REMARKS

Entry of the foregoing and favorable reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.116, and in light of the remarks which follow, are respectfully requested.

By the present amendment, claim 22 has been canceled. Applicants reserve their rights to file a continued prosecution application directed to the canceled subject matter. Claim 15 has been amended to recite that the polypeptide is expressed "for at least 90 days after administration of said composition". Support for this amendment appears at least on page 7 of the application as filed. Applicants submit that no new matter has been added via this amendment.

Priority Claim

Applicant requests that the Examiner acknowledge the claims for priority under 35 U.S.C. § 120 and 35 U.S.C. § 119(d). Applicant submitted a certified copy of the priority document on September 27, 2000.

35 U.S.C. § 103(a)

Claims 15, 18, 19 and 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Perricaudet et al. in view of Quantin et al. and Rice et al. and further in view of Ordahl et al. Claim 22 has been cancelled, rendering the rejection of this claim moot. For the following reasons, this rejection is respectfully traversed with respect to the other pending claims.

Perricaudet et al. teach using adenoviral vectors under the control of the adenoviral major late promoter in association with the tripartite leader sequence to express a coding sequence. In this respect, Perricaudet et al. teach that the intramuscular injection into mice of a β-galactosidase-encoding recombinant adenovirus resulted in an efficient infection of skeletal muscle cells and expression of the transduced β-galactosidase gene for several days post infection.

Note that although Perricaudet et al. mention the successful expression of a β-galactosidase encoding recombinant adenovirus, there is no mention of how this construct was made nor any mention of the promoter used. There is no disclosure in Perricaudet et al. that long

term expression of the adenoviral vector in muscle cells can be achieved. Indeed, several days means that expression was achieved more than two, but not many.

Quantin et al. teach a β-galactosidase-encoding recombinant adenoviral vector under the control of a mouse skeletal α-actin promoter reinforced by an enhancer from a mouse myosin light chain gene (MLC1-3F). Quantin et al. disclose that β-galactosidase expression was detected in myogenic cells lines from mouse (C2.7) and rat (L6) 24 hours after injection and in newborn mice muscle 12 days after injection.

Rice et al. disclose an E1-deleted adenovirus containing in place of the E1 sequences either on HIV-1 LTR fused to a cat gene or, as control RSV LTR fused to the cat gene. These two recombinant constructs were infected into HeLa cells and HeLa tat cells and CAT mRNA was detected 36 hours post injection.

Applicants respectfully submit that Rice is not pertinent since there is no reason why a person skilled in the art would equate HELA cells with muscles cells. In fact, HELA cells were derived from a 1952 cell line obtained from a human cervical carcinoma. Cervical carcinoma cells are quite different from muscle cells. Therefore, a person skilled in the art would not have any expectation of success that the adenoviral vector described in Rice et al. could be modified and expressed in muscle cells.

In addition, Rice is directed to a study of tat gene of HIV and its effect on the HIV gene activation. In Rice, the RSV LTR was selected as a control promoter because it was insensitive to tat . One of skill in the art would not be motivated to use the teachings of Rice et al to use a RSV LTR region in an adenoviral construct for use in muscle cells because these constructs used in Rice were expressed in very different cells and for the very different purpose of being insensitive to the tat gene product of HIV.

Ordahl et al. teach using the plasmid pRSVcat as a control to compare expression with the cTNT promoters. Plasmid pRSVcat is thus only a reporter plasmid, which cannot be compared in size with an adenoviral vector, which is much larger. Ordahl et al. teach that the avian sarcoma virus, LTR, which is isolated from a naturally occurring carcinoma of a chicken can be expressed in chicken muscle cells *in vitro*. Ordahl et al. do not suggest to the person skilled in the art to use an adenoviral vector. Rather, at column 4, lines 60 to 62 only suggest plasmids, viruses, retroviruses and naked nucleotide sequences.

A person skilled in the art would realize that there are many different types of viruses including, for instance, parvovirus, picornavirus, papovavirus, reovirus, togavirus, coronavirus, paramyxovirus, rhabdovirus, orthomyxovirus, herpesvirus, poxvirus and the like. There is no suggestion in Ordahl et al. to use a specific adenoviral vector and absolutely no teaching how to construct such a recombinant vector for expression in muscle cells.

The combination of Perricaudet et al. and Quentin et al. in view of Rice et al. and Ordahl et al. fail to render the presently claimed invention obvious, since the only successful teaching of *in vivo* expression in muscle cells is that of Quantin et al. which adenoviral construct shows successful expression of the heterologous β-galactosidase in muscle cells using an enhancer of the mouse MLC1-3F gene and a mouse skeletal α-action promoter. Thus, only a muscle specific promoter was successfully used in the prior art to express β-galactosidase *in vivo* for 12 days post injection.

However, even if a skilled artisan would seek a non-muscle specific promoter to substitute in the adenoviral vector of Quantin et al. or Perricaudet et al., there would not be any expectation of success that a non-muscle specific promoter can be used to express a heterologous nucleotide sequence *in vivo*, especially to achieve long-term expression; i.e., beyond 3 months (90 days).

Moreover, none of the cited prior art references disclose or suggest that long term expression of the heterologous polynucleotide sequence can be achieved; i.e., for at least 90 days, as presently claimed. This is an unexpected result that is not achieved in the prior art.

More specifically, it should be noted by the Examiner that:

1. Perricaudet et al. teaches expression only for several days in muscle cells.
2. Quantin et al. teaches achieving expression only 12 days.
3. Rice et al. measures expression 36 hours post injection in HeLa cells.
4. Ordahl et al. measures expression of CAT after 24 hours.

Thus, none of the references suggest expression of a heterologous polynucleotide sequence for a duration of at least 90 days.

Moreover, the mere fact that the LTR from RSV is deemed to be a strong promoter as disclosed in Ordahl et al. does not mean to the person skilled in the art that expression of a heterologous polynucleotide can be achieved over a long duration of time in muscle cells.

Thus, since none of the prior art references illustrate or even suggest that expression of a polypeptide in muscle cells using the defective adenoviral vector can be achieved for at least 90 days after administration the presently claimed invention, with its surprising properties should be considered unobvious over the cited prior art.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claim 17 has been rejected under 35 U.S.C. § 103(a) as being obvious over Perricaudet et al. in view of Rice et al. and Ordahl et al. and further in view of Nabel et al. For the following reasons, this rejection is respectfully traversed.

Perricaudet et al., Rice et al. and Ordahl et al. were discussed extensively above and the same arguments apply in this rejection and care incorporated herein by reference.

Nabel et al. does not remedy the deficiencies of the other references with respect to claim 17 that is dependent from claim 15.

Although Nabel et al. generally disclose using an adenoviral vector to deliver genes encoding proteins with thrombolytic properties, there is no disclosure concerning the length of time of which expression of the protein are achieved.

Therefore, the combination of Perricaudet et al., Quantin et al., Rice et al., Ordahl et al. and further in view of Nabel et al. fail to render the presently claimed invention obvious due to the fact that long-term expression of at least 90 days of heterologous polynucleotide in muscle cells *in vivo* was never demonstrated in any of these references. Thus, a person skilled in the art would not have any expectation of success that long term expression can be achieved.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Obviousness-Type Double Patenting

Claims 15 and 17-19 have been rejected under the judicially created doctrine of obviousness-type double patenting. Applicants request that this rejection be held in abeyance until there is allowable subject matter. At that time, Applicants will proceed by filing a terminal disclaimer.

Summary

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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MARKED UP-VERSION TO SHOW CHANGES MADE

IN THE CLAIMS:

15. (Fifth time Amended) A composition comprising (i) a non replicative recombinant adenoviral vector wherein said non replicative recombinant adenoviral vector comprises a heterologous polynucleotide sequence encoding a polypeptide, which polynucleotide sequence is inserted into a deleted E1 region of said non replicative recombinant adenoviral vector and is under the control of a promoter selected from the promoter contained in the Long Terminal Repeat of Rous Sarcoma Virus, the promoter of the IE gene of cytomegalovirus, the Mouse Mammary Tumor Virus inducible promoter and the metallothionine promoter wherein said polypeptide is expressed *in vivo* in muscle cells for at least 90 days after administration of said composition and is distributed throughout the muscle mass;

and (ii) a pharmaceutically acceptable carrier.